Darunavir (DRV, Prezista)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Tablets: 75 mg, 150 mg, 400 mg, and 600 mg

Dosing Recommendations

DRV should not be used without ritonavir (RTV).

Neonate/infant dose:
DRV is not approved for use in neonates/infants.

Pediatric dose:
DRV should not be used in pediatric patients <3 years of age.

3 to <6 years of age:
Safety and efficacy have not been established.

6 to <18 years of age and body weight ≥20 kg:

Weight (kg)	Dose DRV + RTV (both twice daily* with food)
≥20 to <30 kg	DRV 375 mg + RTV 50 mg (0.6 ml of 80 mg/ml)†
≥30 to <40 kg	DRV 450 mg + RTV 60 mg (0.8 ml of 80 mg/ml)†
≥40 kg	DRV 600 mg + RTV 100 mg

** Do not use once-daily dosing in children <12 years of age or in any patient <18 years of age who is treatment experienced. Once-daily dosing (DRV 800 mg + RTV 100 mg) may be used in treatment naive pediatric patients 12–18 years of age and body weight >40 kg (see Pediatric Use).*

† To enhance palatability, RTV 100 mg twice daily as the tablet formulation may be safely substituted for the liquid formulation, even though the RTV dose is higher.

Adolescent (≥18 years of age)/adult dose (treatment naive or antiretroviral [ARV] experienced with no DRV mutations):
DRV 800 mg + RTV 100 mg, both once daily with food.

Selected Adverse Events

- Skin rash (DRV has a sulfonamide moiety. Stevens-Johnson syndrome [SJS] and erythema multiforme have been reported.)
- Hepatotoxicity
- Diarrhea, nausea
- Headaches
- Possible increased bleeding in patients with hemophilia
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- Administer DRV with food, which increases area under the curve (AUC) and maximum plasma concentration (C_{max}) by 30%. Drug exposure is not significantly altered by the calorie and fat content of the meal.
- DRV contains a sulfa moiety. The potential for cross sensitivity between DRV and other drugs in the sulfonamide class is unknown. Use DRV with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires administration of multiple 75-mg or 150-mg tablets to achieve the recommended doses of 375 mg or 450 mg depending on weight band. Pill burden may have a negative effect on adherence.
- Store DRV at room temperature (25°C or 77°F).

Metabolism

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate.
- **Dosing in patients with hepatic impairment:** DRV is primarily metabolized by the liver. No

Adolescent (≥18 years of age)/adult dose (treatment experienced with at least one DRV mutation):
DRV 600 mg + RTV 100 mg, both twice daily with food.

data exist for dosing adult patients with varying degrees of hepatic impairment; caution should be used when administering DRV to such patients. DRV is not recommended in patients with severe hepatic impairment.

- **Dosing in patients with renal impairment:** No dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min). No pharmacokinetic (PK) data exist in patients with severe renal impairment or end-stage renal disease.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- ***Metabolism:*** Darunavir is primarily metabolized by CYP3A4. Ritonavir inhibits CYP3A4, thereby increasing the plasma concentration of darunavir. There is the potential for multiple drug interactions with darunavir.
- Before darunavir is administered, the patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities:

- *More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.
- *Less common:* Skin rash, including erythema multiforme and SJS, has been reported. Fever and elevated hepatic transaminases have been reported. Lipid abnormalities.
- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors (e.g., hepatitis B or hepatitis C virus coinfection, baseline elevation in transaminases).

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/DRV.html).

Pediatric Use: Food and Drug Administration (FDA) approved for use in children 6 years of age and older as part of combination antiretroviral therapy (cART).

Initial pediatric pharmacokinetic (PK) evaluation was based upon a randomized, open-label, multicenter study that enrolled 80 treatment-experienced pediatric participants 6 to <18 years of age and weighing ≥20 kg. The participants had a median age of 14 years (range 6 to <18 years); 71% were male; and 54% were white, 30% black, 9% Hispanic, and 8% other race/ethnicity. Patients were stratified according to their weight and received darunavir/ritonavir plus background therapy consisting of at least 2 non-protease inhibitor (PI) ARV drugs[1]. The study was a 2-part Phase II trial to evaluate the PKs and tolerance of darunavir/ritonavir in children. In Part I, a weight-adjusted dose of darunavir 9–15 mg/kg and riton-

avir 1.5–2.5 mg/kg twice daily, equivalent to the standard adult dose of darunavir/ritonavir 600/100 mg twice daily, resulted in inadequate drug exposure in the pediatric population studied with AUC_{24h} of 81% and pre-dose concentration (C_{0h}) of 91% of the corresponding adult PK parameters. A pediatric dose 20%–33% higher than the directly scaled adult dose was needed to achieve drug exposure similar to that found in adults and was the dose selected for Part II of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11–19 mg/kg and ritonavir 1.5–2.5 mg/kg twice daily. This resulted in darunavir AUC_{24h} of 123,276 ng*h/ml (range 71,850–201,520 ng*h/ml) and C_{0h} of 3,693 ng/mL (range 1,842–7,191 ng/ml), 102% and 114% of the corresponding PK values in adults. Patients were stratified by body weight: 20 to <30 kg and 30 to <40 kg. Doses were all given twice daily and were adjusted when patients changed weight categories. After the 2-week PK evaluation all patients were allowed to switch to ritonavir 100-mg capsules if desired to avoid the use of liquid oral ritonavir.

Based on the findings in the safety and efficacy portion of the study, weight band doses of darunavir/ritonavir were chosen as follows: 375/50 mg twice daily for body weight 20 to <30kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥40 kg. This treatment was safe and effective.

Note that 27 of the 80 participants in this study[1] switched from the ritonavir liquid formulation to ritonavir 100-mg capsules, which are much easier to tolerate for children who can swallow pills. A separate study in 19 Thai children[2] (http://www.retroconference.org/2011/Abstracts/40772.htm) used ritonavir 100 mg twice daily as the boosting ritonavir dose, with darunavir doses of 375 mg (body weight 20 to <30 kg), 450 mg (body weight 30 to 40 kg), and 600 mg twice daily (body weight ≥40 kg). The PKs of those twice-daily darunavir doses boosted with 100 mg ritonavir twice daily showed values similar to those obtained with lower ritonavir doses. This regimen was well tolerated and adds further support to boosting with the easier to tolerate 100-mg capsule of ritonavir twice daily even in children as young as 6 years of age or weighing as little as 20 kg.

An investigational darunavir oral suspension has been studied in children 3 to <6 years of age and weighing 10 to <20 kg[3] (http://www.retroconference.org/2011/Abstracts/42411.htm). Higher than anticipated doses were required to achieve target drug exposures. Diarrhea and vomiting were the most common side effects. There was good efficacy through 48 weeks in this treatment-experienced population.

Although darunavir is approved for once-daily dosing in ARV-naive adults, it should not be used once daily in children younger than 12 years of age because of more rapid clearance and absence of pediatric data. However, once-daily dosing (DRV 800 mg + RTV 100 mg) may be considered in treatment naive adolescents 12–17 years of age and body weight >40 kg based upon a small study (N=12) that showed good Week 24 virologic responses and PK parameters similar to those seen in adults treated with once-daily darunavir[4].

References

1. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS.* 2009;23(15):2005-2013.
2. Chokephaibulkit K, Prasithsirikul W, et al. Pharmacokinetics of DRV/r in Asian HIV-1+ 6-Year-old Children. Paper presented at: 18th Conference on Retroviruses and Opportunistic Infections (CROI); February 27–March 2, 2011 Boston, MA. Abstract 714.
3. Violari A, Bologna R, et al. ARIEL: 24-Week Safety and Efficacy of DRV/r in Treatment-experienced 3- to <6-Year-old Patients. Paper presented at: 18th Conference on Retroviruses and Opportunistic Infections (CROI); Boston, MA. Abstract 713.
4. Flynn P, Blanche S, Giaquinto C, et al. 24-week efficacy, safety, tolerability and pharmacokinetics of darunavir/ritonavir once daily in treatment-naïve adolescents aged 12 to < 18 years in DIONE. 3rd International Workshop on HIV Pediatrics, July 15-16, 2011. Abstract # PP_2.